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Structure–property relationship of quinuclidinium surfactants—Towards multifunctional biologically active molecules

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ABSTRACT

Motivated by diverse biological and pharmacological activity of quinuclidine and oxime compounds we have synthesized and characterized novel class of surfactants, 3-hydroxyimino quinuclidinium bromides with different alkyl chains lengths (C_nQNOH; n = 12, 14 and 16). The incorporation of non conventional hydroxyimino quinuclidinium headgroup and variation in alkyl chain length affects hydrophilic-hydrophobic balance of surfactant molecule and thereby physicochemical properties important for its application. Therefore, newly synthesized surfactants were characterized by the combination of different experimental techniques: X-ray analysis, potentiometry, electrical conductivity, surface tension and dynamic light scattering measurements, as well as antimicrobial susceptibility tests. Comprehensive investigation of C_nQNOH surfactants enabled insight into structure-property relationship *i.e.*, way in which the arrangement of surfactant molecules in the crystal phase correlates with their solution behavior and biologically activity. The synthesized C_nQNOH surfactants exhibited high adsorption efficiency and relatively low critical micelle concentrations. In addition, all investigated compounds showed very potent and promising activity against Gram-positive and clinically relevant Gram-negative bacterial strains compared to conventional antimicrobial agents: tetracycline and gentamicin. The overall results indicate that bicyclic headgroup with oxime moiety, which affects both hydrophilicity and hydrophobicity of C_nQNOH molecule in addition to enabling hydrogen bonding, has dominant effect on crystal packing and physicochemical properties. The unique structural features of cationic surfactants with hydroxyimino quinuclidine headgroup along with diverse biological activity have made them promising structures in novel drug discovery. Obtained fundamental understanding how combination of different functionalities in a single surfactant molecule affects its physicochemical properties represents a good starting point for further biological research.

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1. Introduction

Surfactants are organic compounds containing in one molecule both lyophobic (hydrophobic) and lyophilic (hydrophilic) parts. In solutions surfactants self-assemble in the variety of three-dimensional nano and micro structures like micelles, vesicles and liquid crystalline phases [1]. Different surfactant phases are of interest in pharmaceutical applications either as drug carriers or as targeted drug delivery systems [2–4].

Contemporary investigations in surfactant science are driven by the requirements to design surfactants that possess enhanced physicochemical properties and can be utilized in complex systems as well as for specific applications in modern technologies [5–11]. On the other hand, there has been increased interest in the development of drugs with polypotent chemical structures which result in interaction with various molecular targets or receptors and multifunctionality [12]. Due to their functionalities drug molecules themselves often behave as surfactants. Nano structures formed by

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self-assembling of biologically active amphiphilic molecules can be at the same time efficient therapeutics as well as nano carriers.

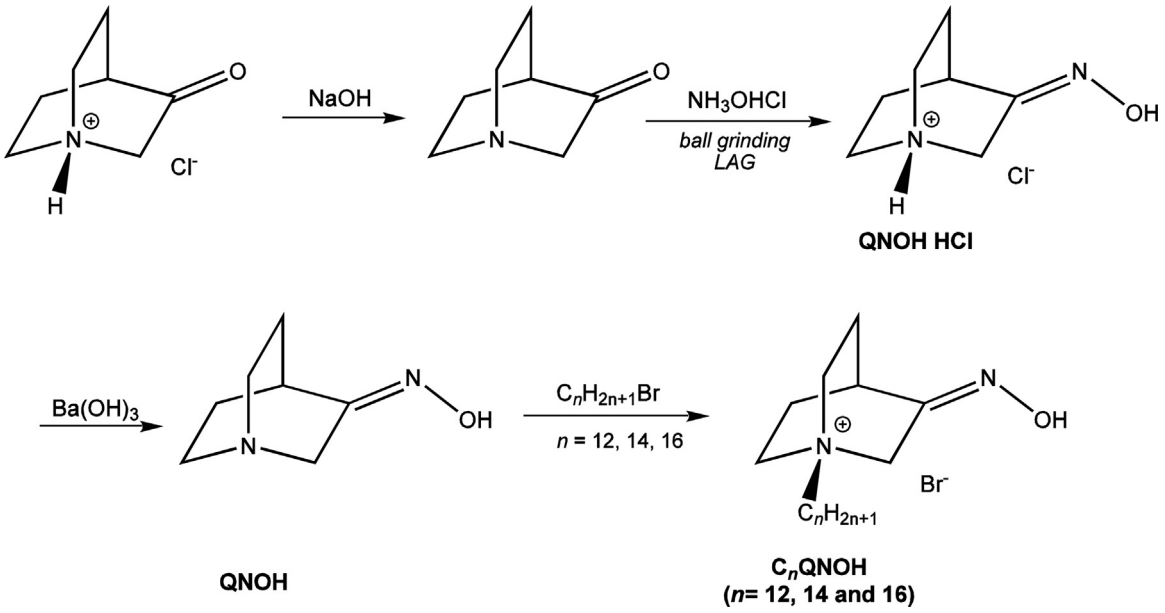
A class of compounds that has been attracting increased attention in modern drug discovery is the quinuclidine based derivatives. The quinuclidine is a saturated bicyclic alkaloid found in several plant-based natural products with a broad spectrum of biological activities: (i) a large number of quinuclidine-based compounds are found to be an attractive isostere of lipid-lowering agents which inhibit squalene synthase activity, leading to reduced cholesterol biosynthesis in animals [13,14], (ii) they are also identified as promising classes of anticancer agents against several cancer cell lines [15], (iii) it has been demonstrated that several quinuclidine scaffolds, including arylquinuclidine have potent activity against parasitic protozoa in concentrations varying from the nanomolar to subnanomolar range [16–18].

Oximes and their complexes are another class of compounds that have recently drawn compelling interest owing to their biological and pharmacological activities. Oximes have been recognized as valuable structures for many important pharmaceutical and synthetic chemistry applications, and often act as chemical building blocks for the synthesis of some relevant antimicrobial and antihypertensive agents as well as insectides [19,20]. Besides that, oximes and oxime functionalized surfactants have been firstly reported as compounds with a great potential in the treatment of organophosphorus compounds poisoning, including insecticides and nerve agents, by acetylcholinesterase (AChE) reactivation [21,22]. Several 3-substituted quinuclidinium derivatives, including quinuclidinium oximes, showed antidotal efficacy as a result of their interaction with AChE and/or other receptors in the cholinergic system *e.g.*, suppression of presynaptic synthesis of acetylcholine [23,24].

Despite considerable interest for quinuclidine and oxime functionalities, studies of surfactants containing these moieties are scarce. In order to obtain oxime functionalized surfactants and estimate their physicochemical properties Singh et al. have synthesized and characterized 3-hydroxyiminomethyl-1-alkylpyridinium bromides [25]. Hydrophobized derivatives of 1,4-diazabicyclo[2.2.2]octane, which are cationic surfactants with quinuclidinium headgroup, have been investigated by Zakharova et al. [26]. Dymond and Attard investigated vastly different cationic amphiphiles as modulators of membrane curvature elastic stress [27]. They have shown that alkylquinuclidinium compounds exhibit good cytotoxic efficacy towards HL-60 cells. Studies by differential scanning calorimetry and Raman spectroscopy showed that alkylquinuclidinium bromides exhibit two or three thermal phase transitions depending on alkyl chain length [28]. Recently, Bhadani et al. investigated self-aggregation and liquid crystalline behavior of ester-functionalized quinuclidinium surfactants [29]. They showed that physicochemical properties of these surfactants are greatly affected by unique structure of quinuclidinium headgroup.

Motivated by diverse biological and pharmacological activity of quinuclidine and oxime compounds we have prepared and characterized novel series of homologous 3-hydroxyimino quinuclidinium bromides with different alkyl chains lengths (C_nQNOH, n = 12, 14 and 16, Scheme 1). It was expected that incorporation of nonconventional hydroxyimino quinuclidinium group into the molecular structure of surfactants will take advantage of biological activity of quinuclidinium oximes and amphiphilic nature of surfactant. Since surfactant properties can be tailored by changing hydrophilic-hydrophobic balance of molecule by changing alkyl chain length, the influence of increasing number of C atoms in alkyl chain on physicochemical and biological properties was investigated.

The manner in which surfactant molecules are arranged in the crystal phase correlates with their solution behavior as well as their adsorption and aggregation properties reflects on their biologically activity. Therefore, to establish favorable structure-property relationship is not easy task because it is often difficult to change the surfactant structure in one specific way without changing some of their physicochemical properties in undesirable direction. The structure-property investigations are essential in order to understand the behavior of the complex surfactant systems and to be able to effectively synthesize new surfactants for targeted application. In order to determine structure-property relationship of newly synthesized C_nQNOH surfactants comprehensive characterization from their crystal structure to adsorption and aggregation behavior in solution was performed. In addition, to confirm antimicrobial profile C_nQNOH surfactants were evaluated against a panel of laboratory reference Gram-positive bacteria and clinically relevant antibiotic resistant Gram-negative strains by both disk diffusion and broth microdilution assays. The fundamental understanding



Scheme 1. Schematic representation of synthesis route for 3-hydroxyimino quinuclidinium surfactants with increasing alkyl chain length (C_nQNOH).

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